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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/732,680	12/08/2000	Martin Adamczewski	Mo-6000/LeA 34,147	2900

34469 7590 02/13/2004

BAYER CROPSCIENCE LP
Patent Department
100 BAYER ROAD
PITTSBURGH, PA 15205-9741

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/732,680	ADAMCZEWSKI ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *06 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: RAW SEQUENCE LISTING ERROR REPORT

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/6/03 has been entered.

Claims 42 and 43 are pending in the Application.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s) set forth in the attached Raw Sequence Listing Error Report. Applicant indicated in the response of 11/6/03, that no Raw Sequence Listing Error Report was received in the previous Office Action, so the problem could not be addressed. Against the possibility that the Error Report is again separated from the Office Action, the following is a description of the problem: SEQ ID NOS: 3 and 4 contain 'i' residues, but 'i' is invalid in the Sequence Listing. Instead Applicant should use 'n' and provide an explanation of the source of the genetic material in the <220>-<223> section.

Objections Withdrawn

The objection to the oath is withdrawn in view of Applicant's arguments.

Claim Rejections - 35 USC § 112

Claims 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 42 and 43 are drawn to methods of identifying compounds that affect the conductance of acetylcholine receptors by contacting with test compounds one of the following 4 compositions:

from claim 42,

1) a host cell comprising an acetylcholine receptor comprising SEQ ID NO:2 or a fragment thereof,

or from claim 43:

2) a host cell that is transfected with a nucleic acid encoding SEQ ID NO:2 or a fragment thereof,

3) a polypeptide of SEQ ID NO:2 or a fragment thereof,

4) an acetylcholine receptor comprising SEQ ID NO:2 or a fragment thereof.

Claim 42 requires detection of the altered conductive property, claim 43 requires only measurement of binding.

The specification teaches that SEQ ID NO:2 is a beta type acetylcholine receptor from the insect Drosophila. A working example, is presented at page 16 of the specification in which Xenopus oocytes are transfected with expression vectors encoding Drosophila alpha 1 and alpha 3 subunits and SEQ ID NO:2. After incubation for three to five days, the currents through the oocyte membrane were measured using whole-cell discharges. Cells were stimulated with acetylcholine (10 micromolar). Immediately after the stimulus, inward currents were measured, (see FIG. 1). The specification does not disclose the nature of the currents, and it is not clear from Fig. 1 what type of ion was transported.

The prior art teaches that Xenopus oocytes comprise acetylcholine receptors and that oocyte membranes are depolarized by acetylcholine concentrations as low as 1 nM. See e.g. Kusano et al (J. Physiol. 328: 143-170, 1982), page 143, item 4. In view of this, and the failure of the specification to disclose any control experiment, it is not clear that the depolarization observed by Applicant was due to acetylcholine receptors comprising Drosophila subunits as opposed to Xenopus acetylcholine receptors native to the oocyte. The prior art also teaches that formation of acetylcholine receptors composed of recombinantly expressed Drosophila receptor subunits is highly unpredictable, and had not been achieved in any cell including Xenopus oocytes and cultured Drosophila cells as of 1997. See Lansdell et al (J. Neurochem. 68(5):1812-1819, 1997), entire document, especially abstract. Given the teachings of the prior art and the failure of the specification to adequately identify the type of current observed or to disclose control experiments accounting for the native Xenopus acetylcholine

receptor activities, there is reason to doubt the assertion in the specification that the currents obtained in the working example were due to an acetylcholine receptor comprising SEQ ID NO:2, or that such a receptor was assembled in the oocyte. In view of Landsdell (1997) who taught that Drosophila acetylcholine receptors could not be made by recombinant expression of subunits in either Xenopus oocytes or insect cells, one of skill in the art could not use the claimed invention because one could not make functional receptors from Drosophila subunits as taught by the instant specification.

It is further noted that after the time of filing, Lansdell et al (J. Neurochem. 80: 1009-1018, 2002) disclose a 441 amino acid acetylcholine receptor subunit from Drosophila that appears to be identical to SEQ ID NO:2. These authors demonstrated coassembly of this subunit with other Drosophila subunits, but were unable to assemble functional acetylcholine receptors using Drosophila subunits. Also, while showing that hybrid receptors comprising SEQ ID NO:2 and vertebrate beta subunits could bind radioligands, these authors did not report any measurement of conductivity from these hybrid receptors. This post-filing disclosure supports the conclusion that the formation of acetylcholine receptors from recombinantly expressed Drosophila subunits is highly unpredictable, and casts doubt on the significance of the result in the working example.

Even if Applicant is able to show that the results in the working example are significant, the claims would still lack full enablement for the following reasons. The first two methods of claim 43 do not require the formation of an acetylcholine receptor, and embrace methods of identifying, solely on the basis of binding affinity to SEQ ID NO:2 or a fragment thereof, compounds that affect receptor conductivity. The specification

does not provide any guidance as to what portions of SEQ ID NO:2 are available to bind to test compounds, and which are not. Because SEQ ID NO:2 is a transmembrane protein that apparently interacts with other acetylcholine receptor subunits, one of skill in the art appreciates that when it is a member of a receptor, some of its domains are not available to bind to test compounds because they are sequestered in the membrane or otherwise occluded by interaction with other receptor subunits. So, one of skill in the art would reasonably expect that compounds that bound to a lone SEQ ID NO:2 polypeptide or fragment would not necessarily affect acetylcholine receptor conductivity as required by the claims, because the binding sites for some of these compounds would be unavailable in the presence of the other subunits and/or the cell membrane. Furthermore, there is no evidence of record that indicates that binding to SEQ ID NO:2 should affect conductivity for any reason, i.e. there is no evidence that all conductivity characteristics are not mediated by binding sites on other subunits. Methods of identifying compounds that affect receptor conductivity, but that require only measuring binding to SEQ ID NO:2 or its fragments, are incomplete methods because they recite no steps that require measurement of conductance of any receptor, and the specification has not taught which portions of SEQ ID NO:2, if any, must be bound in order to affect the conductivity of a receptor comprising SEQ ID NO:2 or its fragments.

Claims 42 and 43 also embody methods in which SEQ ID NO:2 or its fragments are incorporated into receptors, and binding or conductance is measured. These methods are not limited as to the composition of the receptors, except that they must include SEQ ID NO:2 or its fragments. As noted above, Landsdell et al (1997) taught

that formation of acetylcholine receptors composed of recombinantly expressed Drosophila receptor subunits is highly unpredictable, and had not been achieved in any cell including Xenopus oocytes or cultured Drosophila cells as of 1997. See abstract. In view of the established unpredictability of the art, should Applicant show that the results from the working example are significant, then the enabled scope of the invention would be limited to methods that use the receptor subunits used in the working example, i.e. Drosophila alpha 1 and alpha 3 subunits in combination with SEQ ID NO:2 or its fragments.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42 is indefinite because it recites "the at least one compound" without antecedent basis. Deletion of the words "at least" is suggested.

Claim 43 is indefinite because the method steps are not concordant with the purpose set forth in the preamble. The claim is directed to a method of determining a compound that binds to an acetylcholine receptor and alters its conductive property. However, the method steps fail to recite any step at which the conductive property is measured, and instead require measurement only of binding to the receptor.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 42 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Elliott et al (WO 95/13299, issued 18 May, 1995).

Elliott teaches methods of identifying compounds that modulate the activity of human nicotinic acetylcholine receptors by expressing the receptor subunits in cells, contacting the cells with test compounds and measuring the effects on electrical current across the cell membrane. See page 39, line 10 to page 40, line 10. Elliott also teaches methods of measuring the binding of test compounds to the an acetylcholine receptor subunit. See paragraph bridging pages 41 and 42, and claim 10 on page 49. The instant claims are embrace nucleic acids that encode fragments of a polypeptide having an amino acid sequence as set forth in SEQ ID NO:2. This language can be interpreted as reading on nucleic acids that encode polypeptides that contain a short regions of identity with SEQ I DNO:2. Elliot teaches a polypeptide that comprises a sequence fragment of SEQ ID NO:2 and nucleic acids encoding the polypeptide. See SEQ ID NOS: 1 and 2 of Elliott in which amino acids 18-21 are identical to a fragment consisting of amino acids 360-363 of instant SEQ ID NO:2.

Thus Elliott anticipates the claims. This rejection can be overcome by amending the claims to require that the polypeptide encoded by the nucleic acid must consist of SEQ ID NO:2 or a fragment thereof.

Conclusion

No claim is allowed.

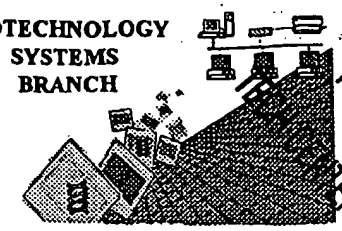
Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.

BIOTECHNOLOGY SYSTEMS BRANCH



RECEIVED
FEB 26 2003
TECH CENTER 1600/2900

RAW SEQUENCE LISTING ERROR REPORT

The Biotechnology Systems Branch of the Scientific and Technical Information Center (STIC) detected errors when processing the following computer readable form:

Application Serial Number: 09/732,680B
Source: 1600
Date Processed by STIC: 2/20/2003

THE ATTACHED PRINTOUT EXPLAINS DETECTED ERRORS.
PLEASE FORWARD THIS INFORMATION TO THE APPLICANT BY EITHER:

1) **INCLUDING A COPY OF THIS PRINTOUT IN YOUR NEXT COMMUNICATION TO THE APPLICANT, WITH A NOTICE TO COMPLY or,**
2) **TELEPHONING APPLICANT AND FAXING A COPY OF THIS PRINTOUT, WITH A NOTICE TO COMPLY**

FOR CRF SUBMISSION QUESTIONS, PLEASE CONTACT MARK SPENCER, 703-308-4212.

FOR SEQUENCE RULES INTERPRETATION, PLEASE CONTACT ROBERT WAX, 703-308-4216.
PATENTIN 2.1 e-mail help: patin21help@uspto.gov or phone 703-306-4119 (R. Wax)
PATENTIN 3.0 e-mail help: patin3help@uspto.gov or phone 703-306-4119 (R. Wax)

TO REDUCE ERRORED SEQUENCE LISTINGS, PLEASE USE THE **CHECKER VERSION 3.1 PROGRAM**, ACCESSIBLE THROUGH THE U.S. PATENT AND TRADEMARK OFFICE WEBSITE. SEE BELOW FOR ADDRESS:
http://www.uspto.gov/web/offices/pac/checker

Applicants submitting genetic sequence information electronically on diskette or CD-Rom should be aware that there is a possibility that the disk/CD-Rom may have been affected by treatment given to all incoming mail.
Please consider using alternate methods of submission for the disk/CD-Rom or replacement disk/CD-Rom.
Any reply including a sequence listing in electronic form should NOT be sent to the 20231 zip code address for the United States Patent and Trademark Office, and instead should be sent via the following to the indicated addresses:

1. EFS-Bio (<http://www.uspto.gov/ebc/efs/downloads/documents.htm> , **EFS Submission User Manual** - ePAVE)
2. **U.S. Postal Service:** U.S. Patent and Trademark Office, Box Sequence, P.O. Box 2327, Arlington, VA 22202
3. **Hand Carry directly to:**
   U.S. Patent and Trademark Office, Technology Center 1600, Reception Area, 7th Floor, Examiner Name, Sequence Information, Crystal Mall One, 1911 South Clark Street, Arlington, VA 22202
   Or
   U.S. Patent and Trademark Office, Box Sequence, Customer Window, Lobby, Room 1B03, Crystal Plaza Two, 2011 South Clark Place, Arlington, VA 22202
4. **Federal Express, United Parcel Service, or other delivery service t** : U.S. Patent and Trademark Office, Box Sequence, Room 1B03-Mailroom, Crystal Plaza Two, 2011 South Clark Place, Arlington, VA 22202

Revised 01/29/2002

Raw Sequence Listing Error Summary

ERROR DETECTED | **SUGGESTED CORRECTION** | SERIAL NUMBER: 09/732,680B

ATTN: NEW RULES CASES: PLEASE DISREGARD ENGLISH "ALPHA" HEADERS, WHICH WERE INSERTED BY PTO SOFTWARE

1____ Wrapped Nucleics / Wrapped Aminos — The number/text at the end of each line "wrapped" down to the next line. This may occur if your file was retrieved in a word processor after creating it. Please adjust your right margin to .3; this will prevent "wrapping."

2____ Invalid Line Length — The rules require that a line not exceed 72 characters in length. This includes white spaces.

3____ Misaligned Amino Numbering — The numbering under each 5th amino acid is misaligned. Do not use tab codes between numbers; use space characters, instead.

4____ Non-ASCII — The submitted file was not saved in ASCII(DOS) text, as required by the Sequence Rules. Please ensure your subsequent submission is saved in ASCII text.

5____ Variable Length — Sequence(s)____ contain n's or Xaa's representing more than one residue. Per Sequence Rules, each n or Xaa can only represent a single residue. Please present the maximum number of each residue having variable length and indicate in the <220>-<223> section that some may be missing.

6____ PatentIn 2.0 "bug" — A "bug" in PatentIn version 2.0 has caused the <220>-<223> section to be missing from amino acid sequences(s) _____. Normally, PatentIn would automatically generate this section from the previously coded nucleic acid sequence. Please manually copy the relevant <220>-<223> section to the subsequent amino acid sequence. This applies to the mandatory <220>-<223> sections for Artificial or Unknown sequences.

7____ Skipped Sequences (OLD RULES) — Sequence(s) ____ missing. If intentional, please insert the following lines for each skipped sequence:
(2) INFORMATION FOR SEQ ID NO:X: (insert SEQ ID NO where "X" is shown)
(i) SEQUENCE CHARACTERISTICS: (Do not insert any subheadings under this heading)
(xi) SEQUENCE DESCRIPTION:SEQ ID NO:X: (insert SEQ ID NO where "X" is shown)
This sequence is intentionally skipped

Please also adjust the "(ii) NUMBER OF SEQUENCES:" response to include the skipped sequences.

8____ Skipped Sequences (NEW RULES) — Sequence(s) ____ missing. If intentional, please insert the following lines for each skipped sequence.
<210> sequence id number
<400> sequence id number
000

9 ✓ Use of n's or Xaa's (NEW RULES) — Use of n's and/or Xaa's have been detected in the Sequence Listing.
Per 1.823 of Sequence Rules, use of <220>-<223> is MANDATORY if n's or Xaa's are present.
In <220> to <223> section, please explain location of n or Xaa, and which residue n or Xaa represents.

10____ Invalid <213> Response — Per 1.823 of Sequence Rules, the only valid <213> responses are: Unknown, Artificial Sequence, or scientific name (Genus/species). <220>-<223> section is required when <213> response is Unknown or is Artificial Sequence

11____ Use of <220> — Sequence(s) ____ missing the <220> "Feature" and associated numeric identifiers and responses.
Use of <220> to <223> is MANDATORY if <213> "Organism" response is "Artificial Sequence" or "Unknown." Please explain source of genetic material in <220> to <223> section.
(See "Federal Register," 06/01/1998, Vol. 63, No. 104, pp. 29631-32) (Sec. 1.823 of Sequence Rules)

12____ PatentIn 2.0 "bug" — Please do not use "Copy to Disk" function of PatentIn version 2.0. This causes a corrupted file, resulting in missing mandatory numeric identifiers and responses (as indicated on raw sequence listing). Instead, please use "File Manager" or any other manual means to copy file to floppy disk.

13____ Misuse of n — n can only be used to represent a single nucleotide in a nucleic acid sequence. N is not used to represent any value not specifically a nucleotide.

VERIFICATION SUMMARY DATE: 02/20/2003
PATENT APPLICATION: **US/09/732,680B** TIME: 16:01:52

Input Set : **A:\LeA34147-US.txt**
Output Set: **N:\CRF4\02202003\I732680B.raw**

L:11 M:270 C: Current Application Number differs, Replaced Application Number
L:12 M:271 C: Current Filing Date differs, Replaced Current Filing Date
L:255 M:320 E: (1) Wrong Nucleic Acid Designator, NUMBER OF INVALID KEYS:2
L:267 M:320 E: (1) Wrong Nucleic Acid Designator, NUMBER OF INVALID KEYS:2

1600

RAW SEQUENCE LISTING DATE: 02/20/2003
PATENT APPLICATION: US/09/732,680B TIME: 16:01:51

Input Set : A:\LeA34147-US.txt
Output Set: N:\CRF4\02202003\I732680B.raw

3 <110> APPLICANT: Bayer Aktiengesellschaft
5 <120> TITLE OF INVENTION: Nucleic acids coding for new acetylcholine receptor beta subunits of
6 insects
9 <130> FILE REFERENCE: Le A 34 147
C--> 11 <140> CURRENT APPLICATION NUMBER: US/09/732,680B
C--> 12 <141> CURRENT FILING DATE: 2003-02-13
14 <150> PRIOR APPLICATION NUMBER: DE 199 59 582.8
15 <151> PRIOR FILING DATE: 1999-12-10
17 <160> NUMBER OF SEQ ID NOS: 4
19 <170> SOFTWARE: PatentIn Ver. 2.1

ERRORED SEQUENCES

Does Not Comply
Corrected Diskette Needed

246 <210> SEQ ID NO: 3
247 <211> LENGTH: 20
248 <212> TYPE: DNA
249 <213> ORGANISM: Artificial Sequence
251 <220> FEATURE:
252 <223> OTHER INFORMATION: Primer
254 <400> SEQUENCE: 3
E--> 255 tggcarccit cicartayga 20
258 <210> SEQ ID NO: 4
259 <211> LENGTH: 21
260 <212> TYPE: DNA
261 <213> ORGANISM: Artificial Sequence
263 <220> FEATURE:
264 <223> OTHER INFORMATION: Primer
266 <400> SEQUENCE: 4
E--> 267 catratytty tciccicca t 21

"i" is invalid in the sequence itself. Use "n," instead, and explain in the <2207-<2237 section

same error

See item 9 on Error Summary Sheet